Comparative evidence for the importance of the amygdala in regulating reward salience

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Abstract

Environmental stimuli and life events are often of emotional relevance to the individual. This is due to their recognition and processing by the brain's neural circuits for emotion. In terms of emotion valence, stimuli/events can be neutral (non-emotional), rewarding or aversive. In addition to its basic valence, the salience of an emotional stimulus i.e. how rewarding or how aversive it is, is also of critical importance. Quantitative changes in stimulus reward salience or aversion salience are likely to underlie some major symptoms in stress-related mental disorders. This includes low reward salience as the basis for diminished interest or pleasure in major depressive disorder (MDD) and for apathy (negative symptoms) in schizophrenia, and high aversion salience as the basis for depressed mood in MDD. Insight into the brain region(s) and cellular microcircuits wherein the saliences of reward and aversion stimuli are set is essential for understanding the neurobiology of emotion in health and mental disorders. Here I review the current evidence for the role of the amygdala in processing reward valence and salience, based on studies conducted in human, monkey and, in particular, rat and mouse. Human BOLD-fMRI studies demonstrate amygdala reactivity to reward and its reduction in MDD and schizophrenia. In monkey, some neurons in the basolateral amygdala (BLA) are responsive to reward, aversion, or both. In rat, BLA reward neurons regulate excitation of nucleus accumbens (NAcc) neurons, whereas chronic stress increases intra-amygdala synaptic activity. In mouse, there are BLA glutamatergic principal reward neurons and aversion neurons. Based on this comparative evidence, this review concludes that the mammalian BLA reward neurons could constitute a major contributor to the neural circuitry of reward salience and a critical node in reward pathology.

Keywords	reward; salience; amygdala; reward neuron; stress; depression

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Responses to Reviewer's comments

I have no desire to lengthen the article (which at present is nice and concise, and to the point), or to dictate what should be included or not included. Nevertheless, it might be useful for the author to include some information on what associative learning remains intact after different amygdala manipulations (i.e. what is it that the amygdala is "not doing" in terms of associative learning). In particular, the work of McGaugh and others in the late 1990s might be worth discussing. For example, although BLA lesions impaired conditioned freezing in a simple fear conditioning task in a Y-maze task (BLA lesioned rats would fail to freeze when placed in an arm where they had received shock), these mice were nevertheless perfectly capable of learning to avoid that arm of the maze during free exploration. This suggests that not all learning is impaired after BLA lesions. It might be helpful to contrast what these animals can and cannot learn.

Response: In response to this very important and helpful point, I have added the following text to the end of the section, Amygdala anatomy and aversion processing: "It is important to note that the BLA is less involved in regulating aversive learning about contextual stimuli; for example, rats in which the basolateral complex had been lesioned received footshock in one arm of a Y-maze and whilst they exhibited low levels of freezing behaviour their avoidance of the shock arm was intact [8], with such contextual conditioning occurring primarily in hippocampus [9]."

- Amygdala responds to stimuli of positive (reward) and negative (aversive) valence
- Reduced reward salience is a major and trans-diagnostic psychopathology
- Stress-induced amygdala changes could mediate reduced reward salience
- Amygdala reward neurons constitute a potential target for restoring reward salience

Comparative evidence for the importance of the amygdala in regulating reward salience

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Short title: Amygdala and reward salience

Key words: reward; salience; amygdala; reward neuron; stress; depression

Environmental stimuli and life events are often of emotional relevance to the individual. This is due to their recognition and processing by the brain's neural circuits for emotion. In terms of emotion valence, stimuli/events can be neutral (non-emotional), rewarding or aversive. In addition to its basic valence, the salience of an emotional stimulus i.e. how rewarding or how aversive it is, is also of critical importance. Quantitative changes in stimulus reward salience or aversion salience are likely to underlie some major symptoms in stress-related mental disorders. This includes low reward salience as the basis for diminished interest or pleasure in major depressive disorder (MDD) and for apathy (negative symptoms) in schizophrenia, and high aversion salience as the basis for depressed mood in MDD. Insight into the brain region(s) and cellular microcircuits wherein the saliences of reward and aversion stimuli are set is essential for understanding the neurobiology of emotion in health and mental disorders. Here I review the current evidence for the role of the amygdala in processing reward valence and salience, based on studies conducted in human, monkey and, in particular, rat and mouse. Human BOLD-fMRI studies demonstrate amygdala reactivity to reward and its reduction in MDD and schizophrenia. In monkey, some neurons in the basolateral amygdala (BLA) are responsive to reward, aversion, or both. In rat, BLA reward neurons regulate excitation of nucleus accumbens (NAcc) neurons, whereas chronic stress increases intra-amygdala synaptic activity. In mouse, there are BLA glutamatergic principal reward neurons and aversion neurons. Based on this comparative evidence, this review concludes that the mammalian BLA reward neurons could constitute a major contributor to the neural circuitry of reward salience and a critical node in reward pathology.

Amygdala anatomy and aversion processing

The amygdala is located in the temporal lobe and comprises a complex of subcortical nuclei. In knowledge obtained primarily from rodent studies, it is a major brain region in the neural circuitry of emotion in terms of: inputs received from sensory regions e.g. sensory thalamus, sensory cortex; cellular and microcircuit responding to innate emotional stimuli; learning about and storing memories for the association between neutral to-be-conditioned stimuli and innate emotional stimuli; instigating output of heterogeneous but integrated emotional responses. In terms of emotion valence, research that has provided the current understanding of amygdala function has focussed almost exclusively on aversion. A number of the multiple nuclei that comprise the amygdala are involved [1]. The lateral (LA), basolateral (BLA) and basomedial (BMA) nuclei are often grouped together as the basolateral complex. They have a cortex-like cytoarchitecture, with the neuron population containing about 80% glutamatergic spiny principal neurons and 20% GABA interneurons of various types including parvalbumin- or somatostatin-expressing interneurons [2 •]. The learning paradigm of Pavlovian fear conditioned freezing has been utilized to study amygdala microcircuitry for processing aversion

valence stimuli. The LA receives inputs from thalamic and cortical sensory sub-regions relaying innate aversive stimuli (e.g. footshock, predator odour), as well as neutral stimuli (e.g. tone) that become conditioned due to temporal coincidence with an innate stimulus [3]. In terms of cell firing activity, both principal neurons and GABA interneurons in the LA are responsive – either as excitation or inhibition – to both innate and conditioned aversive stimuli [4]. The LA principal neurons project to glutamate principal neurons and GABA interneurons in the BLA. Aversive-stimulus induced activation of the LA leads to firing of some BLA principal neurons – the latter are referred to as fear neurons in the case that the eliciting stimulus is a tone conditioned to footshock [5]. The central nucleus of the amygdala (CeA) comprises the capsular CeA (CeC) and lateral (CeL) and medial (CeM) divisions of CeA [1]. The CeA is made up of GABA neurons; in the CeL these resemble the medium spiny neurons of the striatum; indeed, each CeA division resembles the striatum in containing relatively few local-circuit (inter)neurons [1,2 •,6]. It has been widely assumed that the LA and BLA principal neurons responsive to aversive valence stimuli project to GABA neurons in CeL and CeM [2 •]. However, recently it was proposed that these BLA aversion neurons actually project to GABA neurons in the CeC, and the latter then project in turn to CeL and CeM GABA neurons [6,7••]. Furthermore, it has recently been demonstrated that CeL, CeM and CeC GABA neurons also receive projections from BLA principal neurons responsive to reward valence stimuli [6,7••] (see below). With regard to CeA output, the CeM GABA neurons are the major output projectors to regions, e.g. periaqueductal gray, important in the neural circuitry of behavioural and physiological emotional responses. It is important to note that the BLA is less involved in regulating aversive learning about contextual stimuli; for example, rats in which the basolateral complex had been lesioned received footshock in one arm of a Y-maze and whilst they exhibited low levels of freezing behaviour their avoidance of the shock arm was intact [8], with such contextual conditioning occurring primarily in hippocampus [9].

Human amygdala for reward processing and in emotional disorder

In human and rodent research, the contribution of the ventral tegmental area-nucleus accumbens (VTA-NAcc) dopaminergic mesolimbic pathway to reward processing [10,11] and the contribution of the amygdala to aversion processing ([12]; see previous section), have both received considerable scientific attention. It is only relatively recently that the emphasis has started to shift towards recognising that each of these (and other) brain regions is essential for both reward and aversion processing, and that reward and aversion processing only become distinct at specific levels of neural circuitry [13•]. This shift includes the recognition of the importance of the amygdala in both aversion and reward processing.

In humans, using positron emission tomography (PET) to measure cerebral blood flow, it was demonstrated in healthy subjects that the amygdala responds to happy faces [14 •]. Furthermore,

resting-state PET-blood flow in the amygdala is higher, reflecting increased activity of at least some neurons, in depressed compared with healthy subjects [15]. Using blood oxygen level-dependent (BOLD) fMRI, it was shown that the amygdala is active during exposure to happy versus neutral faces in healthy subjects, and that this response to reward valence stimuli is lower in depressed patients [16]. With regard to neural networks of resting-state functional connectivity in the human brain, the amygdala is considered to contribute to the affective network; this network is involved in emotional processing and regulation at rest, and exhibits altered connectivity between amygdala and other limbic regions in depression [17].

Clearly, there is considerable incentive to increase understanding of the functioning of the amygdala in the neural circuitry of reward processing, as well as of the changes it undergoes in stress-related psychiatric states such as reduced interest or pleasure in major depressive disorder (MDD), and apathy (negative symptoms) in schizophrenia [18].

Amygdala for reward including dedicated reward neurons

As in the human case, the small number of rodent studies of amygdala reward processing have yielded affirmative data [19]. For example, in rats it was demonstrated that LA lesion attenuated amphetamine-induced conditioned place preference [20]. Also in rats, subjects underwent sham- or BLA-lesion and were then trained on an operant response-reward contingency and a stimulus-reward Pavlovian contingency, where reward was sweet food. In subsequent tests, BLA-lesioned rats exhibited attenuated operant responding and reduced Pavlovian-to-instrumental transfer, consistent with an important BLA function in regulating reward valuation [21].

A small number of primate or rodent studies have been conducted in which recording from specific BLA neurons was combined with presentation of reward or aversion cues. In rhesus monkeys, a visual conditioned stimulus (CS) was trace-conditioned to either sweet reward or air-puff aversion (unconditioned stimulus, US), licking and blinking were measured as conditioned responses, and single-unit recording was conducted from neurons in the BLA immediately after US delivery. Some BLA neurons responded with increased firing to reward only, others to aversion only, and some responded to both stimulus valences. Furthermore, some of these 'reward neurons' and 'aversion neurons' responded more when the US was not preceded/announced by the CS i.e. was unexpected, in accordance with prediction error learning theory [22,23]. In rats, one tone CS was conditioned to sucrose delivery in a reward port (CS+ reward) and another tone CS was conditioned to footshock (CS+ aversion); during the CS, single-unit recording was conducted from neurons in LA, BLA, BMA or CeA. In terms of increases in firing, 23% of neurons were responsive to CS+ reward specifically, 19% to CS+ aversion specifically, and 26% were responsive to both CS+ reward and CS+ aversion; 7% of neurons responded to both CS+ but the change in firing was in the opposite direction to CS+ reward and CS+

aversion [24]. Also in rat, using region-specific pharmacological inhibition it was demonstrated that: BLA neurons are essential for tone CS+ reward to elicit reward-directed behaviour; some BLA neurons exhibit increased and prolonged firing in response to CS+ reward; some nucleus accumbens (NAcc) neurons exhibit increased and prolonged firing in response to CS+ reward; the increased, prolonged firing in NAcc neurons is dependent on functional BLA neurons; increased, prolonged firing in NAcc neurons is also dependent on dopamine projections from the ventral tegmental area (VTA). These findings suggest that BLA reward-neuron projections to NAcc neurons are essential for the latter, in the concurrent presence of dopamine facilitation, to promote reward-directed behaviour [25 ••].

Moving onto mouse studies, reward as intra-peritoneal nicotine administration or aversion as footshock were studied in terms of effects on expression of c-Fos, the protein encoded by the immediate-early gene *c-fos*, in neurons of anterior BLA; in both cases about 6% of neurons were activated. A lentivirus encoding light-sensitive channelrhodopsin2 (ChR2) under the control of the *c-fos* promoter was injected into anterior BLA; this allowed for the study of whether BLA neurons were specifically responsive to a reward or aversion US or a CS that predicted it, and also whether optogenetic stimulation of these valence-specific neurons elicited valence-specific behaviour. Mice were placed in a compartmentalized chamber, exposed to nicotine or footshock to induce ChR2 expression, and in one specific compartment an odour CS was paired with optogenetic stimulation. Mice exposed to nicotine spent more time in (i.e. preferred) this compartment and mice exposed to footshock avoided this compartment. With regard to operant behaviour, mice exposed to nicotine learned an operant response to optogenetically self-stimulate their BLA reward neurons. Valence-specific behaviours were dependent on responsive BLA neurons, both when either the US (unconditioned response) or the CS (conditioned response) provided the stimulus [26].

Two recent mouse studies provide further evidence for the existence and function of reward neurons and aversion neurons in BLA [7 ••,27 ••]. In one study [27 ••], NAcc and CeM were selected as candidate projection regions for BLA reward and aversion neurons, respectively, and retrograde labelling was used to identify BLA projectors. Mice were exposed to Pavlovian reward or fear conditioning; whole-cell patch-clamp recording was conducted for retrograde-labelled neurons in brain slices to determine the AMPA receptor/NMDA receptor ratio, a proxy for glutamatergic synaptic strength. BLA-NAcc neurons showed a ratio increase in mice that had been reward conditioned and a ratio decrease in mice that had been fear conditioned, and the opposite relationships held for BLA-CeM neurons. Using optogenetics to excite BLA neurons, mice were tested in an operant paradigm wherein nose-poking activated the optical fibre: BLA-NAcc neuron self-stimulation reinforced nose-poking whereas BLA-CeM neuron self-stimulation did not. When mice were tested in a Pavlovian paradigm wherein entering one of two compartments activated the optic fibre, BLA-CeM activation resulted in avoidance of this compartment. With respect to the anterior-posterior topography of NAcc

and CeM projectors across the anterior-posterior extent of BLA, there was no evidence of clear separation [27 ••].

In another study [7 ••], using a RNA-binding protein, expression of which depended on neural activity to switch on the *c-fos* promoter, it was possible to conduct RNA immunoprecipitation specific to activated neurons. The emotional stimuli used were a female mouse and footshock, to target reward and aversion neurons, respectively. Microarray transcriptome expression was conducted to identify specific marker genes for these two neuron types: *Ppp1r1b* (encoding DARPP-32) was enriched in reward neurons and *Rspo2* (encoding R-spondin 2) was enriched in aversion neurons. In terms of BLA anterior-posterior topography, *Ppp1r1b*$^+$ neurons were localized in the posterior (parvocellular) BLA and *Rspo2*$^+$ neurons were localized in the anterior (magnocellular) BLA (Fig. 1A). c-Fos protein expression was used to confirm that posterior BLA neurons were reward sensitive and anterior BLA neurons aversion sensitive. Neuron type-specific optogenetic inhibition was used to demonstrate that reward conditioning was dependent on active *Ppp1r1b*$^+$ neurons and fear conditioning on active *Rspo2*$^+$ neurons. Effects of neuron type-specific optogenetic excitation on conditioning were also studied: *Ppp1r1b*$^+$ neuron self-stimulation reinforced nose-poking whereas *Rspo2*$^+$ neuron activation promoted contextual fear conditioning. With regard to candidate projection regions, retrograde tracer was injected into NAcc, CeM/CeL or CeC: BLA-NAcc neurons were 70% *Ppp1r1b*$^+$ reward neurons localized in posterior BLA and 30% *Rspo2*$^+$ aversion neurons localized in anterior BLA; BLA-CeM/CeL neurons were, surprisingly, nearly 100% *Ppp1r1b*$^+$ reward neurons localized in posterior BLA; and BLA-CeC neurons were nearly 100% *Rspo2*$^+$ aversion neurons localized in anterior BLA [7 ••].

These two important mouse studies, building on monkey and rat evidence, concur in demonstrating that the mouse BLA contains neurons that are essential in regulating either reward valence or aversion valence. However, they differ in their findings with respect to the anterior-posterior topography and the projection regions of the reward and aversion neurons, and these discrepancies will require clarification studies.

(INSERT FIGURE 1 ABOUT HERE)

Basolateral amygdala reward neurons and the processing of reward salience

Therefore, whilst the critical details of the micro-circuitry of the BLA reward neurons and aversion neurons in terms of topography and projection regions is currently debated, the comparative evidence for existence of exclusively reward-sensitive and exclusively aversion-sensitive BLA neurons is conclusive (Fig. 1A). With regards to function these neurons are stated to be emotion-valence specific. It can be hypothesised that in addition to this, within the emotion valence to which they are sensitive, BLA neurons also determine stimulus salience (Fig. 1B). This can be illustrated by proposing that in the

basal adaptive state the set point of reward neurons on a 3-point salience scale (+++) is "++"whilst the set point of aversion neurons on a 3-point salience scale (- - -) is "-". That is, the average salience attributed to a reward stimulus by BLA reward neurons is "++" and the average salience attributed to an aversion stimulus by BLA aversion neurons is "-". The salience value will be represented in the synaptic and intracellular signalling and firing of reward neurons and aversion neurons. As such, salience value represents a critical stage in determining the strength of the arousal, motivation and behaviour directed towards an environmental stimulus/life event, thereby resembling the affective state value function previously proposed for the BLA [28]. Then, to give the concept of salience value clinical significance, following a period of stress the set point of reward neurons on their salience scale decreases to "+" and that of aversion neurons on their salience scale increases to "- -/- - -" (Fig. 1C). That is, the same reward is now less salient and the same aversion is now more salient than in the basal adaptive state; subsequently, on average, reward stimuli are now less salient than aversion stimuli [12]. That reward neurons and aversion neurons can influence each other's activity has also been demonstrated [7 ••,27 ••], such that stress-induced, coincident shifts in reward and aversion salience might be due to their reciprocal effects on each other's state. This could be achieved via the intervening GABA interneuron micro-circuits [6,7 ••] (Fig. 1A). This would be consistent with the simultaneous occurrence of decreased interest in daily activities and increased depressed mood and focus on aversion, a common state in MDD [18].

Stress, amygdala and reward salience

Chronic exposure of animals to stress in the form of uncontrollable and/or unpredictable aversive stimuli allows for the study of its effects on amygdala function and could well provide important insights into amygdala pathophysiology in emotional disorders. Whilst chronic stress has been demonstrated to induce increased sensitivity to aversion in amygdala-dependent behavioural paradigms e.g. Pavlovian fear conditioning [29] and decreased sensitivity to reward [30-32], there have been few studies of chronic stress effects on amygdala function. In rats, the effects of repeated restraint stress across 9 days were investigated in terms of LA or BLA principal neuron activity using in vivo intracellular recording. Relative to controls, stressed rats showed an increase in the frequency of spontaneous excitatory synaptic events, which correlated with the number of dendritic spines in reconstructed neurons and is likely to result in increased neuronal output [33,34]. These effects could be analogous to the increased amygdala activity observed in human depression; however, the valence sensitivity and projection regions of these neurons remain to be determined.

Conclusions

There has been a relative lack of progress in discovering much-needed novel molecular targets and developing more effective treatments for stress-related mental disorders. To a large extent, paucity of knowledge of the neural circuitry underlying major psychological processes accounts for this lack of progress. In particular, this concerns the cellular and molecular changes in specific brain regions impacted by environmental and epigenetic aetiological factors that constitute the pathophysiology underlying major psychopathologies. The research domain criteria (RDoC) framework, which emphasizes the research importance of specific psychological domains and dimensions rather than complex mental disorder diagnostic entities, has provided new impetus for translational research across human subjects and animal models [35,36]. The positive valence systems domain includes dimensions such as reward valuation, reward expectancy, reward learning and responsiveness to reward attainment (www.nimh.nih.gov/research-priorities/rdoc/). The concept of amygdala-mediated reward salience, as proposed here, is clearly of direct relevance to these RDoC dimensions and the pathologies thereof. This theoretical advance, combined with the practical advances in the molecular tools available for the study of specific brain regions, cell types and intra-cellular processes in animal models, constitutes an important opportunity for future testing of specific hypotheses related to the neuro-biology, -pathology and -pharmacology of reward salience and its disruption.

Conflict of interest statement

Nothing declared.

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•• of outstanding interest

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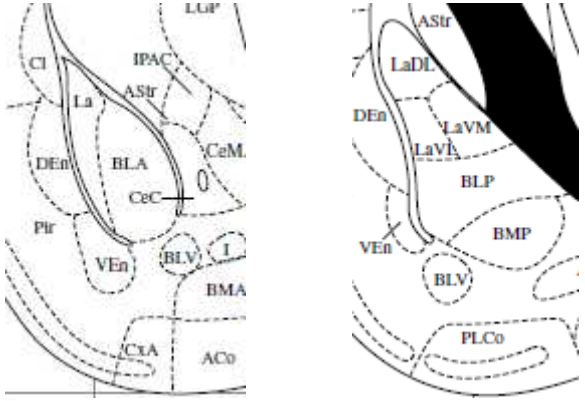
Figure legend

Figure 1. A model of the basolateral amygdala as a major regulator of emotional stimulus salience. (A) Upper: Representative figures from Franklin and Paxinos [37] depicting the mouse amygdala in coronal section. Left panel, relatively anterior amygdala showing lateral nucleus (LA) and anterior (magnocellular) basolateral nucleus (BLA). Right panel, relatively posterior amygdala showing posterior (parvocellular) basolateral nucleus (BLP). Lower: Proposed microcircuit (based on [7 ••,27 ••]) of basolateral amygdala comprising principal glutamate reward neurons (green) concentrated in

posterior basolateral amygdala, principal glutamate aversion neurons (red) concentrated in anterior basolateral amygdala, and GABA interneurons (blue) connecting reward and aversion neurons. Reward neurons receive inputs from LA principal glutamate neurons concerning innate/unconditioned reward stimuli (R-US) or stimuli conditioned to reward (CS), and aversion neurons receive inputs from LA principal glutamate neurons concerning aversion US (A-US) or CS. Projections shown are for reward neurons to nucleus accumbens (NAcc) and aversion neurons to capsular central amygdala (CeC). (B) In the basal state, basolateral amygdala reward neurons and aversion neurons are excited by their respective LA neuron inputs and their excitation signals the emotional valence of a stimulus. Furthermore, the extent of excitation signals the emotional salience of the stimulus. On average, reward neurons are set to be more excited by reward (++) than aversion neurons are by aversion (-). (C) In the chronic stress state, synaptic and intracellular signalling and firing of reward neurons are decreased, such that the same reward stimulus now has less emotional salience (+). Conversely, synaptic and intracellular signalling and firing of aversion neurons are increased, such that the same aversion stimulus now has more emotional salience (--). On average, reward neurons are now less excited by reward than aversion neurons are by aversion. GABA interneurons could mediate concurrent changes in the excitability of these two neuron types.

(A)


Cl
IPAC
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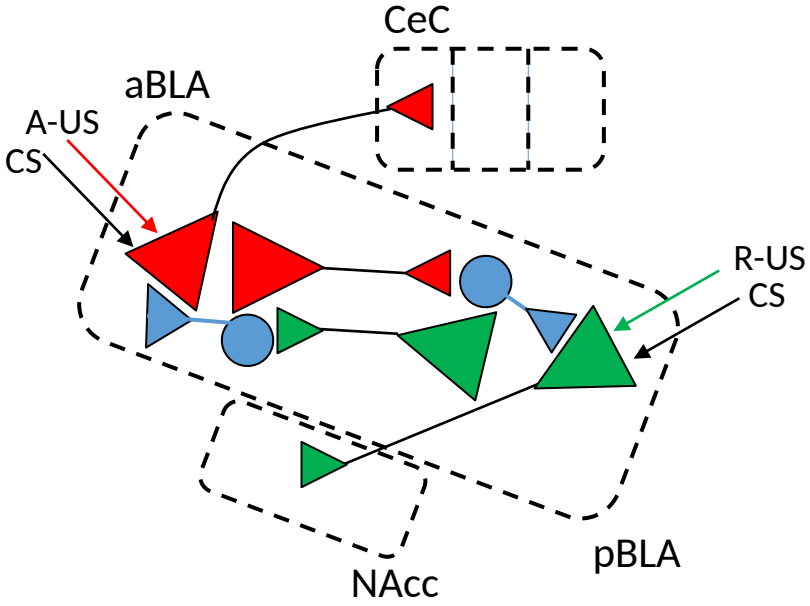
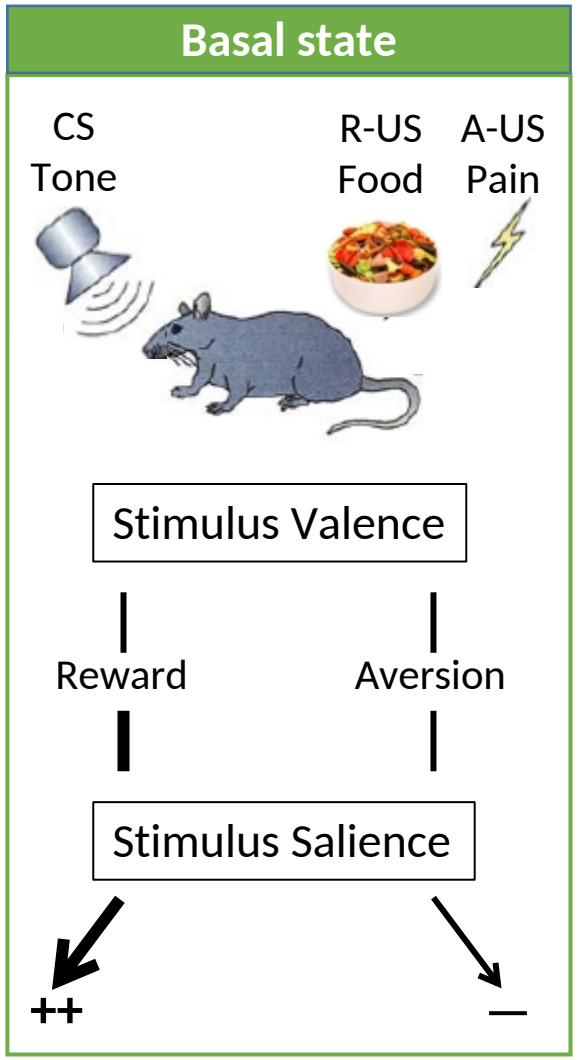

CeC
aBLA
A-US
CS
R-US
CS
NAcc
pBLA

(B)


Basal state
CS
Tone
R-US
Food
A-US
Pain
Stimulus Valence
Reward
Aversion
Stimulus Salience
++
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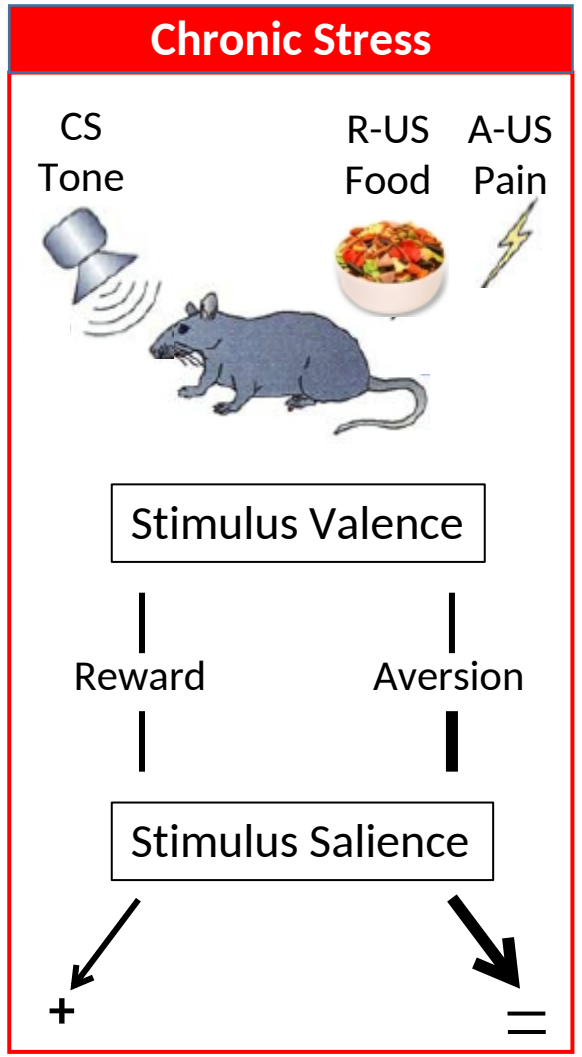
(C)


Chronic Stress
CS
Tone
R-US
Food
A-US
Pain
Stimulus Valence
Reward
Aversion
Stimulus Salience
+
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